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(Bedside to Bench Report)

Two cases of recurrent ovarian clear cell carcinoma treated with sorafenib

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Running title: **Sorafenib treatment of OCCC**

Number of Figure; 4

Abstract

Sorafenib is an oral multikinase inhibitor targeting Raf and other kinases. The anti-tumor effect of sorafenib is thought to be mediated through its inhibition of the RAS-Raf-Erk pathway, as well as its inhibition of VEGFR and PDGFR. Sorafenib has been effective at treating patients with renal cell carcinoma (RCC). Ovarian clear cell carcinoma (OCCC) is a chemoresistant subtype of ovarian cancer. OCCC is represented by cells with clear cytoplasm that resemble those observed in RCC. Using a microarray database, the gene expression profile of OCCC was similar to that of RCC. The effects of sorafenib against human OCCC are unknown. Therefore, we used sorafenib to treat two patients with recurrent chemoresistant OCCC, and observed good effect in both of them without severe side effects. We believe that sorafenib is an effective agent against OCCC. Given the chemoresistant nature of this tumor, this drug appears to be very valuable.

KEYWORDS: sorafenib, ovarian clear cell carcinoma, progression-free survival

Introduction

Sorafenib is an oral multikinase inhibitor targeting Raf and other kinases (i.e., vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), Flt3, and c-KIT). The anti-tumor effect of sorafenib is thought to be mediated through its inhibition of the RAS-Raf-Erk pathway ¹, which is involved in cell proliferation, as well as its inhibition of VEGFR and PDGFR, which play a role in angiogenesis ^{2, 3}. Sorafenib has been effective at treating patients with renal cell carcinoma (RCC) ⁴ and hepatocellular carcinoma (HCC) ⁵.

Ovarian clear cell carcinoma (OCCC) has a specific gene expression profile ⁶, and is a chemoresistant histological subtype of ovarian cancer. OCCC is represented by cells with clear cytoplasm that resemble those observed in RCC. Using a microarray database, we previously reported that the gene expression profile of OCCC was similar to that of RCC, and we showed good effects of sorafenib in a mouse model of OCCC ⁷.

The effects of sorafenib against human OCCC are unknown. Therefore, we attempted to use sorafenib to treat two patients with recurrent chemoresistant OCCC. This is the first case report to evaluate sorafenib efficacy against OCCC.

Case Description

We used sorafenib monotherapy (400 mg/day, orally) in two patients with

recurrent and chemoresistant OCCC after written informed consents were obtained. The efficacy of the treatment was judged based on progression-free survival for at least six months (RECIST 1.1). These clinical studies had been approved by the institutional review board (IRB) of Kyoto University in advanced.

Clinical case 1

A 63-year-old Japanese postmenopausal female, with 1 gestation and 0 parturitions, who complained of dull lower abdominal pain and distension, visited our hospital. A 15 cm cystic tumor containing solid parts was detected in the lower abdomen. Total abdominal hysterectomy (TAH) with a bilateral salpingo-oophorectomy (BSO), pelvic/para-aortic lymphadenectomies (PELA/PALAs) and omentectomy were performed. After the surgery, an OCCC of stage Ia (PT1a, N0, M0) was diagnosed. Due to the early stage of the disease and her complication of IgA nephropathy, adjuvant chemotherapy was omitted. Thirteen months after the primary surgery, recurrent nodes 2 cm in diameter appeared in the ascending colon and the omentum. After resections of these recurrent nodes, six courses of irinotecan (90 mg/m² x 2)/cisplatin (60 mg/m²) combination chemotherapy were administered.

After one year, however, disseminated nodes and swelling of the lymph nodes were widely observed in the abdomen. Six courses of paclitaxel (175 mg/m²)/carboplatin (AUC 6) combination chemotherapy were added. After six months, the recurrent peritoneal tumors had grown vigorously.

Accordingly, the patient was administered 800 mg/day of sorafenib. The patient experienced a hand-foot skin reaction (grade 2, CTCAE v4.0) two weeks later, and subsequently, the dose was decreased to 400 mg/day, which was continued for six months. The sizes of the lymph nodes in the hepatic portal region were not significantly different before and after sorafenib monotherapy (Figs 1a, b). The patient's serum levels of CA125 were 200.2 U/ml and 181.2 U/ml before and after treatment, respectively (Fig. 2). The effect of sorafenib was judged to be stable disease (progression-free survival) for six months. The side effects were moderate hand-foot syndrome (grade 2, CTCAE v4.0) and hypertension (160-170 mmHg, grade 2). After sorafenib therapy, the tumor grew again. In spite of oral VP-16 therapy (50 mg/day), the tumor grew vigorously. As a result of DIC, the patient finally died 4.5 years after the primary surgery.

Clinical case 2

A 63-year-old Japanese postmenopausal female, with 3 gestations and 3 parturitions, who visited her neighborhood hospital due to lower abdominal pain, was diagnosed with an ovarian tumor. She was referred to our hospital and a TAH with a BSO, omentectomy, appendectomy, and sampling of the peritoneal nodes/right external iliac lymph nodes, were performed. The main tumor was demonstrated to be 10 cm in diameter, and extended widely into the peritoneal cavity. An OCCC of stage IIIc (PT3c, Nx, M0) was diagnosed. Three courses of intraperitoneal cisplatin (60mg/m²), three courses of intravenous irinotecan (70 mg/m² x 2)/mitomycin (10 mg/body) chemotherapy

and three courses of weekly paclitaxel (50 mg/m²)/carboplatin (90 mg/m²) combination chemotherapy were administered. The residual tumors were markedly reduced, and thus, optimum PELA/PALAs were performed. Six rounds of low-dose cyclophosphamide (230 mg/m²)/ adriamycin (20 mg/m²)/ cisplatin (15 mg/m²) combination chemotherapy were administered monthly.

However, recurrence appeared in the neck lymph nodes. Neck lymphadenectomies were performed, and then, three courses of VP16 (60 mg/m²)/nedaplatin (60 mg/m²) chemotherapy and irradiation (total 50 Gy) of the left neck were administered. For the next four years, five courses of monthly docetaxel (50 mg/m²) / carboplatin (200 mg/m²) chemotherapy, eight courses of irinotecan (60 mg/m² x 2)/cisplatin (50 mg/m²) chemotherapy, six courses of gemcitabine hydrochloride (1000 mg/m² x 2/month) and seven courses of nogitecan hydrochloride (0.5 mg/m² x 5/month) were administered. By eight years after the primary surgery, the mediastinal, axillary and neck lymph nodes had increased by degrees.

The patient then was prescribed 400 mg/day of sorafenib for five months. The sizes of the neck lymph nodes were not significantly different before and after treatment (Figs 3a, b), which was judged to indicate 'stable disease' for six months. The serum levels of CA125 were 193.2 U/ml and 203.5 U/ml before and after the treatment, respectively (Fig. 4). The only side effect was mild hand-foot syndrome (grade1).

After sorafenib therapy, the metastatic neck lymph nodes increased suddenly. External irradiation against the bilateral neck regions (60 Gy), the right axillary lymph nodes (28 Gy) and the para-aortic lymph nodes (30 Gy)

was performed. However, airway narrowing occurred due to swelling of the neck lymph nodes. After a tracheotomy, the patient died due to ileus and bleeding from the bronchi. This was approximately nine years after the primary surgery.

Discussion

Epithelial ovarian carcinoma is histologically divided into serous (OS), endometrioid (OE), mucinous (OM) and OCCC subtypes. OM and OCCC are both commonly considered to be chemoresistant tumors. OCCCs are rare tumors in Europe and the United States ⁸ ; however, they occur often in Japan (20%) ⁹. Therefore, we have searched for agents that are effective against OCCC.

We previously showed that the gene expression profile of OCCC was similar to that of RCC using microarray datasets of ovarian cancer cell lines and human cancer tissues specimens ⁷. We also showed the genes exclusively expressed in OCCC, termed OCCC signature, contained a large gene network consisting of 66 genes, including hepatocyte nuclear factor 1-beta (*HNF1B*) and hypoxia inducible factor 1-alpha subunit (*HIF1A*) ⁶. *HNF1B* is functionally associated with renal morphogenesis ¹⁰. In addition, pathway analysis indicated the Ras-Raf-Erk signaling is activated in OCCC ⁷.

RCC is also a chemoresistant tumor. Sorafenib has recently been approved for RCC, and is considered to be a reasonable molecular targeting

drug against RCC. All sporadic and inherited forms of RCC are associated with mutations in the VHL gene and loss of heterozygosity ^{11, 12}, resulting in the stabilization of the HIF1A protein. HIF1A activates multiple growth factor receptors, such as the EGFR, PDGFR and VEGFR. In addition, increased Ras pathway signaling is observed in RCC ¹³. The anti-tumor effect of sorafenib is thought to be mediated through its inhibition of the RAS-Raf-Erk pathway as well as its inhibition of VEGFR and PDGFR ¹⁻³. We showed that orally administered sorafenib significantly inhibited the growth of RMG-2, a representative OCCC cell line, in nude mice ⁷. We therefore attempted to use sorafenib for human patients with recurrent chemoresistant OCCC.

Both of our patients with OCCC were judged to have 'stable disease' following the use of sorafenib monotherapy and exhibited progression-free survival of at least six months. This suggests that sorafenib is an effective agent against recurrent OCCC. Our two patients were able to continue sorafenib monotherapy (400 mg/day) without severe side effects. Both patients had mild/moderate hand-foot syndrome (grades 1 and 2) and one also had hypertension (grade 2). In fact, we used sorafenib monotherapy for another patient with OCCC for two months. However, therapy had to be stopped due to Trousseau syndrome. The disease was stable for two months, and the side effect was a mild rash (grade 1).

Recently, the Gynecologic Oncology Group reported that sorafenib had modest antitumor activity, but did not provide a sufficient effect as a treatment for ovarian cancer ¹⁴. Fifty-nine patients with measurable

diseases of recurrent ovarian or peritoneal carcinoma were enrolled in this study, but only 14 patients (24%) survived progression-free for six months. This study was conducted mostly for the OS subtype (90%) , whereas only one patient (1.4%) had OCCC. Interestingly, in this study, one of the two patients with partial responses was the patient with OCCC. The data from this study appear to support our result suggesting promising effects of sorafenib against OCCC.

The conventional dose of sorafenib is 800 mg/day^{14,15}. For case 1, we initiated sorafenib treatment with a dose of 800 mg/day, but the dose was soon decreased to 400 mg/day due to hand-foot skin reaction. In a clinical trial conducted for Japanese patients with RCC, dose reduction or therapy interruption due to adverse events was required for as many as 81% of the patients, which is a much higher percentage than for American or European patients ¹⁶. We therefore initiated treatment with a dose of 400 mg/day for case 2. Regardless of the decreased dose, sorafenib showed significant anti-tumor activity in the two OCCC patients.

We believe that sorafenib is an effective agent against OCCC. Given the chemoresistant nature of this tumor, this drug appears to be very valuable. A clinical trial should be performed using sorafenib to treat OCCC. In addition, a further combination regimen¹⁷ using sorafenib may be more effective against OCCC.

Conflict of Interest Disclosures

The authors have no financial conflicts of interest relevant to the present work to declare.

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Legend

Figure 1a & Figure 1b :

The sizes of the lymph nodes in the hepatic portal region were 19.1 mm and 19.5 mm (-30%~+20%; shortest diameter rule, RECIST 1.1), which were not significantly different before (1a) and after (1b) sorafenib monotherapy.

Figure 2 :

Clinical course of the patient and changes in CA125 (case1).

Sorafenib monotherapy suppressed CA125 elevation.

Figure 3a & Figure 3b :

The size of the left neck lymph node was not significantly different before (3a) and after (3b) treatment (14.3, 10.3 mm vs. 14.3, 10.8 mm, respectively (-30%~+20%; shortest diameter rule, RECIST 1.1)).

Figure 4 :

Clinical course of the patient and changes of CA125 (case 2)

Sorafenib monotherapy decreased CA125 level temporarily.

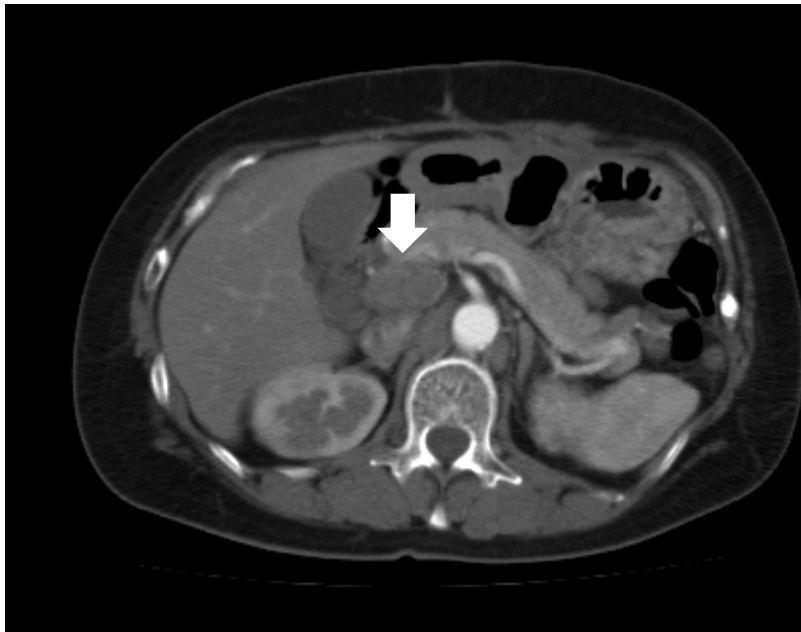


Figure 1a



Figure 1b

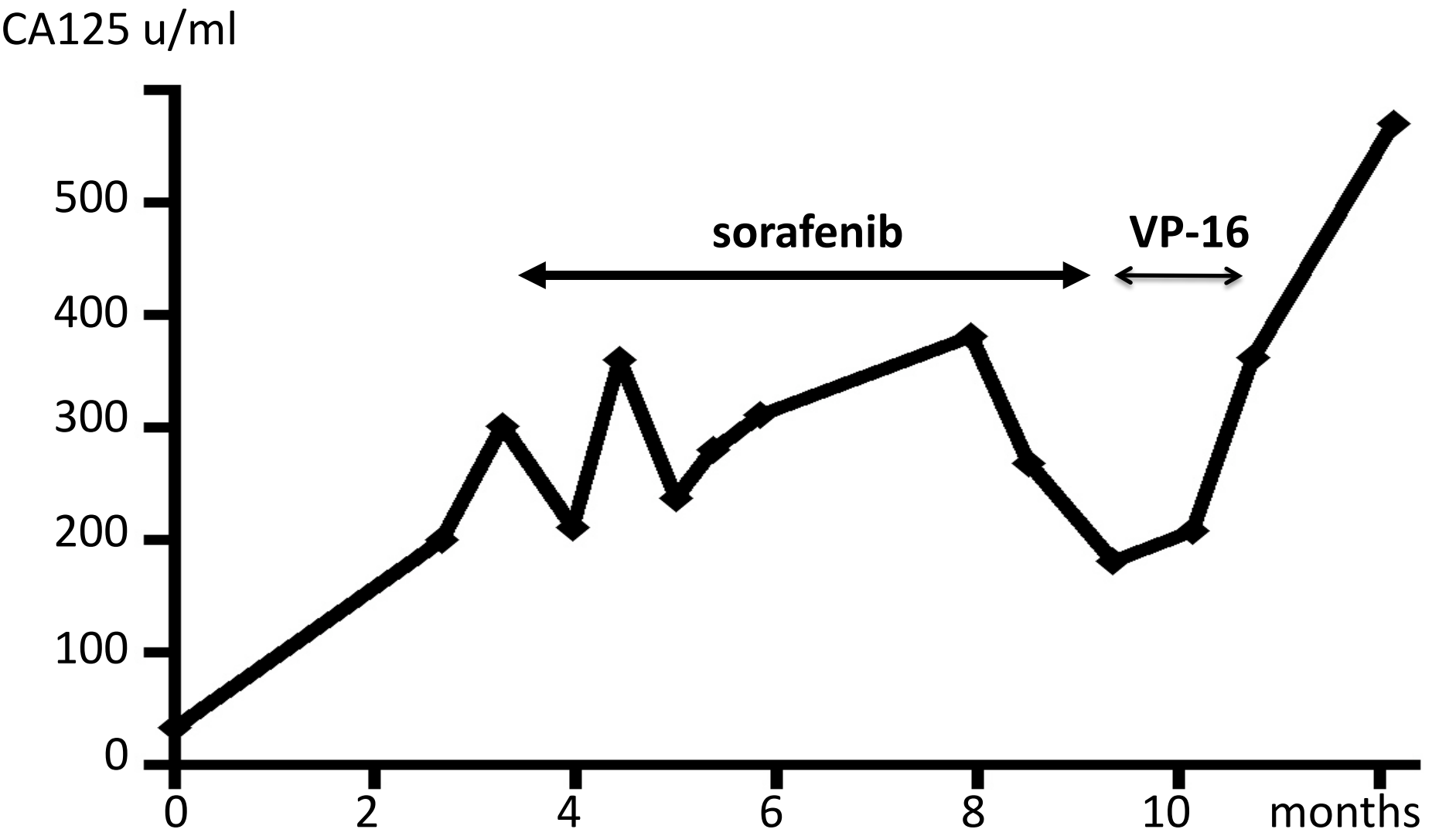


Figure 2

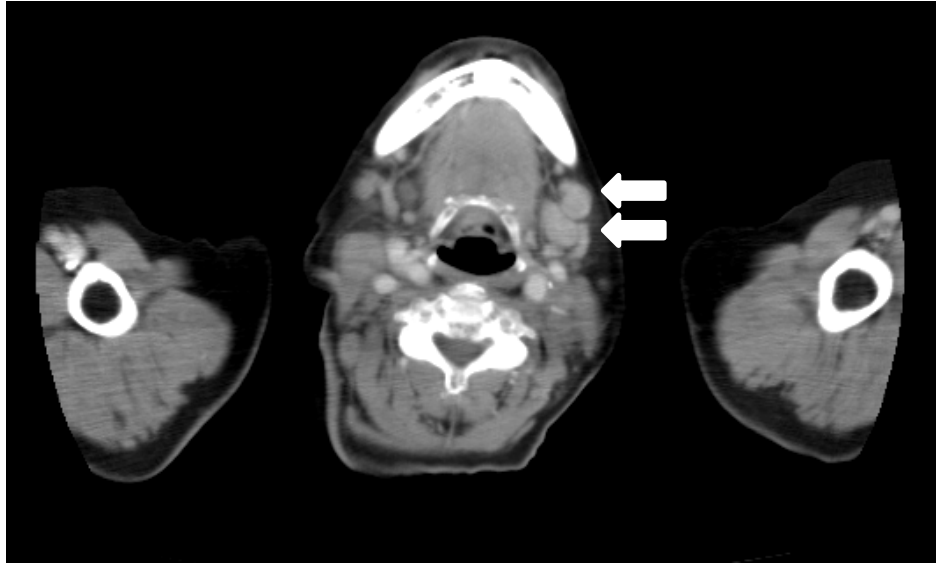


Figure 3a

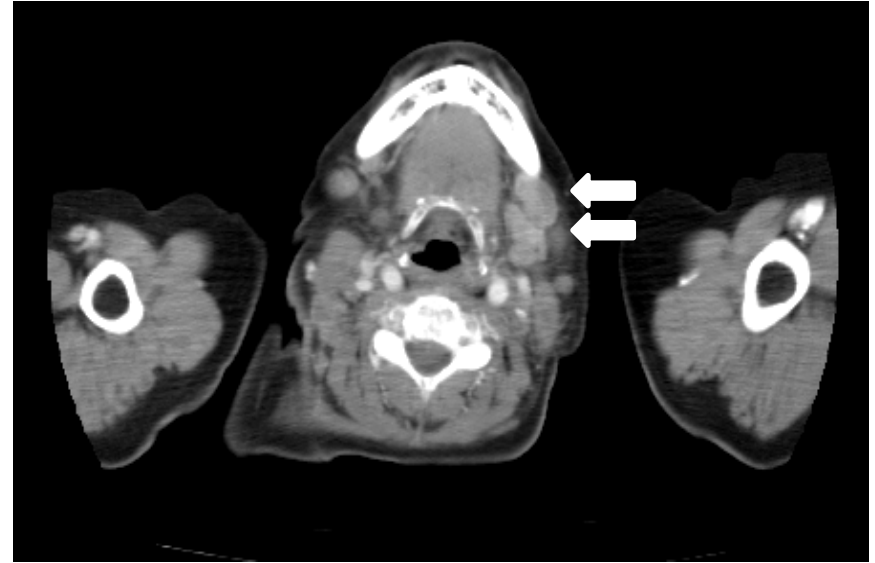


Figure 3b

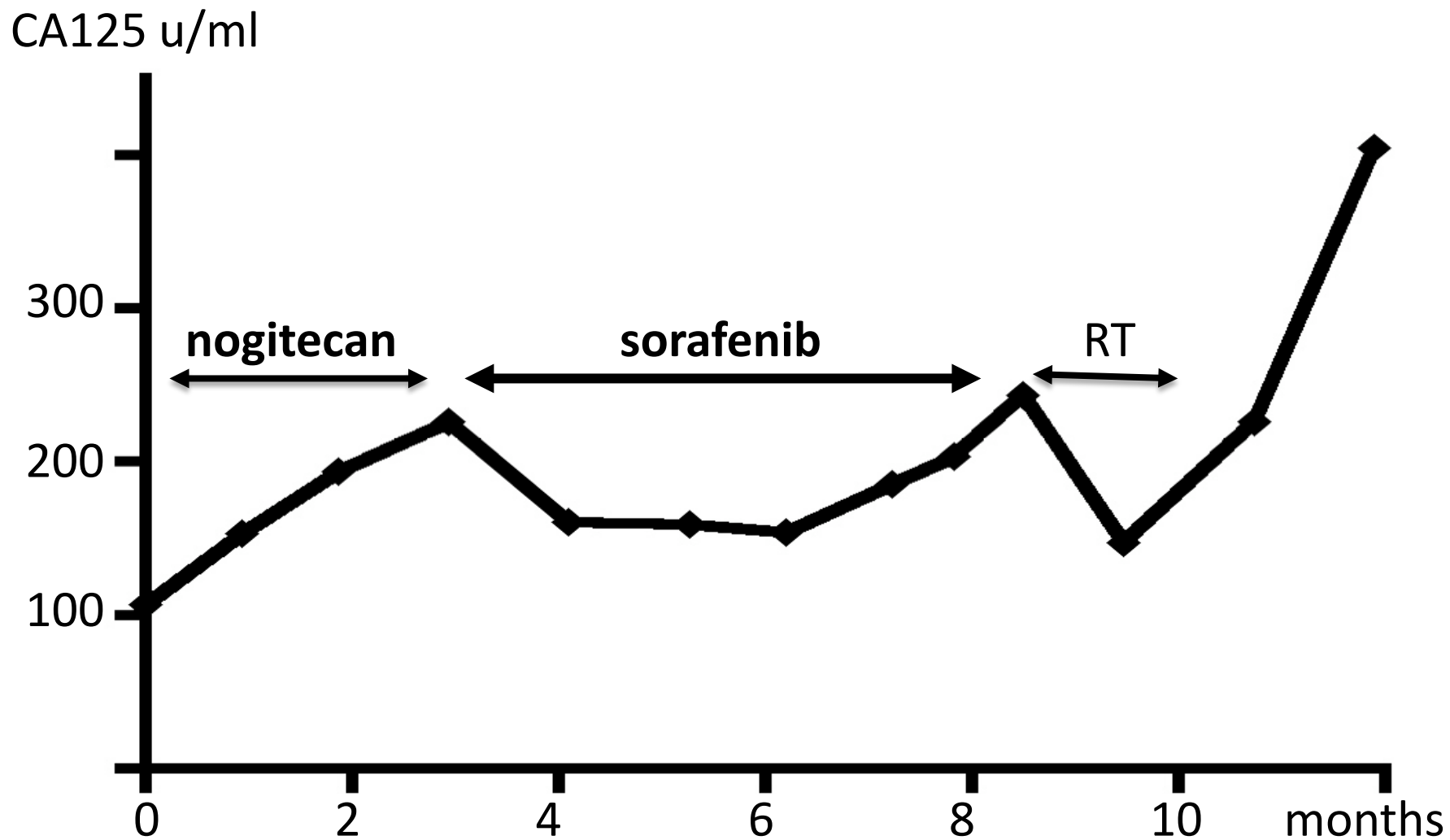


Figure 4